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DIURIL, HYDRODIURIL AND ESIDRIX

DIURIL - Clinical experience with chlorothiazide (Diuril-Merck) since the last Medical Letter appraisal ("pre-publication" issue - December, 1958) confirms the great value of this heterocyclic sulfonamide as an oral diuretic. Its diuretic effectiveness is greater than that of other oral diuretics and it almost equals that of the parenteral mercurials (Annals of N. Y. Acad. Sci., 71:321, 1958). In view of the fact that Diuril is capable of causing serious potassium loss as well as allergic and toxic reactions in a significant number of patients, however, the drug should be used cautiously and the dosage adjusted from time to time to be sure that the minimum effective dose is being used. The following paragraphs bring up to date the material in the earlier review.

USES OF DIURIL - Diuril may be used alone or to supplement mercurials and other diuretics. It is rarely necessary to exceed a dosage of one gram per day, particularly if there is moderate restriction of sodium intake. It is effective in severe as well as mild congestive failure. In nephrosis it may be used to supplement adrenal steroid therapy (its use alone in the presence of the marked albuminuria, low serum protein and low plasma volume of nephrosis may not be advisable). By promoting sodium diuresis, Diuril reduces edema and hypertension in toxemia of pregnancy and acute nephritis. It is effective in some cases of fluid retention caused by cirrhosis of the liver. It is also useful in relieving the edema of corticosteroid therapy when sodium restriction alone is not effective.

Controlled tests are still needed to confirm its usefulness in the management of the syndrome of premenstrual tension, even though it appears to be effective in the treatment of premenstrual edema. In essential hypertension, Diuril exerts a potentiating effect on other antihypertensive drugs; in fact, with usual doses of ganglion-blocking drugs, it may produce an excessive fall in blood pressure. Although Diuril alone does not appear to be helpful for most patients with moderate or severe essential hypertension, its exact place in the management of essential hypertension remains to be established.

POTASSIUM LOSS - With profuse diuresis, Diuril (especially in combined therapy with adrenal steroids) may cause excessive potassium loss as well as alkalosis resulting from excessive loss of chloride. Potassium loss may cause general muscular weakness; it may also aggravate disturbances in heart rhythm

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associated with coronary-artery insufficiency (R. W. Wilkins, JAMA, 167:805, 1958), and it increases the toxicity of digitalis drugs. Hepatic coma and ammonia intoxication have been noted after the use of Diuril in liver cirrhosis.

To reduce the tendency of Diuril to cause electrolyte imbalance, the smallest dose that will have the desired effect should be used, and with prolonged therapy it should be taken in a cycle of two to five days on the drug and two days without it. To combat potassium loss in patients taking Diuril, a supplement of about 4 grams of potassium chloride daily (Potassium Chloride Tablets, U. S. P., 0.3 or 0.5 Gm.) may be needed. To insure absorption of the potassium, either uncoated tablets or a syrup such as liquid Potassium Triplex (Lilly) should be prescribed (1 teaspoonful 4 times daily). Useful food sources of potassium that are also low in sodium are orange and grapefruit juice (about 0.2 Gm. per 4 oz. serving) and bananas (about 0.5 Gm. in an average banana).

Serious sensitivity reactions to chlorothiazide have also occurred. Purpura, with or without thrombocytopenia, has been noted most commonly, but there have been at least two cases of neutropenia, and one fatal case of bone-marrow depression is on record (Zuckerman and Chazan, Brit. Med. J., 2:1338, 1958). These reactions serve as a warning against the indiscriminate or incautious use of this valuable drug.

HYDRODIURIL AND ESIDRIX - Hydrochlorothiazide (Hydrodiuril-Merck; Esidrix-Ciba) differs structurally from chlorothiazide only in the hydrogenation of the double bond in the heterocyclic ring of the latter, but it is effective in much smaller dosage. Effective diuresis, comparable to that produced by 500 mg. of chlorothiazide twice daily, occurs with 50 mg. twice daily. Merck claims that Hydrodiuril may be effective in patients who have become refractory to Diuril, but adequate evidence in support of this claim is not presented. Ciba claims less toxicity and potassium loss for hydrochlorothiazide than for chlorothiazide, but such claims need confirmation. In view of the almost identical pharmacologic action of chlorothiazide and hydrochlorothiazide, therapeutic effects and side actions of the two drugs should prove to be much the same. (The Hydrodiuril package brochure indicates that sensitization effects - "rash or other dermatologic manifestations" - have already been encountered.) Any advantage of Hydrodiuril or Esidrix over Diuril has yet to be demonstrated. Even the cost of equivalent dosages is the same (25 mg. of Hydrodiuril or Esidrix costs the druggist as much as 250 mg. of Diuril and he usually charges the same price).

DRUG COSTS FOR CONTROL OF STREPTOCOCCUS INFECTIONS

How expensive are the drugs used to prevent streptococcus infection and recurrence of rheumatic fever in a patient who has had previous attacks? The question is an important one, since prophylaxis against streptococcus infection should be continuous from the time of the first attack of rheumatic fever until the patient is at least 40 years old; and the difference in the cost of alternative medications for such prophylaxis can mount up, over the years, to several thousand dollars.

To help the physician keep down the financial burden to the patient, The Medical Letter has compared the costs of alternative antibiotics and sulfa drugs, with dosages based mainly on recommendations of the American Heart Association. Alternative medications and costs for the treatment of streptococcus infections and recommendations for the prevention of bacterial endocarditis are also noted. (See "Prevention of Rheumatic Fever and Bacterial Endocarditis through Control of Streptococcal Infections," available free from American Heart Association, 44 East 23rd St., New York 10.)

PROPHYLAXIS AGAINST STREPTOCOCCUS INFECTION - The drug of choice is benzathine penicillin G (Bicillin Long-Acting--Wyeth). A single monthly intramuscular injection of 1, 200, 000 units of this depot form of the antibiotic provides continuous protection (both children and adults get the same dose). Cost (to physician) of 1, 200, 000 units in disposable syringe--about \$2. 50.

Alternative medication--oral penicillin or sulfadiazine (less reliable partly because effectiveness depends on patient's cooperation). Recommended dose of penicillin for both children and adults--200, 000 units once or, preferably, twice daily. The cost to the patient depends largely on how the prescription is written. If the physician prescribes one of the "name" brands of oral penicillin G, the monthly cost to the patient for 60 tablets of 200, 000 units each (purchased in quantities of a hundred) will be about \$9. (The cost in some stores and in some areas for this and other drugs may be lower or higher than the figures given.) If he specifies, or instructs the patient to ask for, a lower-priced brand, the cost will generally run about \$3. 50 to \$4. 50. (All brands, whatever the price, are required by law to contain the labeled quantity and are subject to Food and Drug Administration controls.) If the physician prescribes penicillin V (Pen-Vee Tablets--Wyeth; V-Cillin Pulvules--Lilly), the cost of 60 tablets or pulvules of 200, 000 units each will be about \$15 to \$18. (Penicillin V may at times produce higher blood levels than penicillin G, but there is no proof that penicillin V provides more effective control of streptococcus infections. Penicillin G should be taken on an empty stomach for maximum absorption.) Recommended dose of sulfadiazine--one gram once a day (0. 5 Gm. for children under 60 pounds). The cost of a month's supply for an adult (sixty 0. 5-Gm. tablets) will be about \$3 to \$4. (Reliable information is not available as to the effectiveness of "long-acting" sulfa, sulfamethoxypyridazine [Kynex-Lederle; Midicel--Parke-Davis], in control of streptococcus infections.)

Summary of drug costs for prevention of streptococcus infections

<u>Medication</u>	<u>Quantity for 30 Days</u>	<u>Approximate Cost</u>
Bicillin Long-Acting	1, 200, 000 units	\$2. 50 (to doctor)
Penicillin G	Sixty 200, 000-unit tablets	\$3. 50 to \$9
Penicillin V	Sixty 200, 000-unit tablets or pulvules	\$15 to \$18
Sulfadiazine	Sixty 0. 5-Gm. tablets	\$3 to \$4

TREATMENT OF STREPTOCOCCUS INFECTION - Treatment of an actual infection requires maintenance of effective antibiotic blood levels over a 10-day period. The American Heart Association recommends one intramuscular injection of 900, 000 to 1, 200, 000 units of benzathine penicillin G (600, 000 to

900,000 units for children). Cost of 600,000 units, disposable--about \$1.50; 900,000 units--about \$2.25; cost of 10-cc. vial, 300,000 units per cc.--about \$3.75. Medical Letter consultants believe that benzathine penicillin G provides blood levels which are adequate for prophylaxis, but which may not always be adequate for treatment. They recommend the combination of procaine penicillin G and crystalline penicillin G (300,000 units of procaine penicillin and 100,000 units of crystalline penicillin per cc.), with intramuscular injection of 2 cc. every other day (1 cc. for children). Cost of ten 1-cc. ampules--about \$2.50 to \$4 depending on quantity purchased by physician. (The combination is sold as Crystifor 400-Squibb; Pen-Aqua--Bristol; Pronapen-Pfizer; Penicillin S-R--Parke-Davis; and many other brands.)

Alternative oral antibiotic--The Heart Association recommends 200,000 units of penicillin three times a day for 10 days. Medical Letter consultants suggest a fourth dose at bedtime for greater effectiveness. Cost of 40 tablets of oral penicillin G--\$2.75 to \$9 (per tablet cost is higher than for prophylaxis because smaller quantities are purchased). Cost of 40 tablets or pulvules of oral penicillin V--\$12 to \$18. If the patient is sensitive to penicillin, erythromycin propionate (Ilosone-Lilly) or a tetracycline is recommended (though W. J. Mogabgab and W. Pelon found some types of Group A streptococci resistant to tetracyclines - AMA J. Dis. of Children, 96:696, 1958). Cost of 10-day supply (forty 250-mg. tablets or pulvules)--about \$18 to \$26. (Cost for 1.5 Gm. of tetracycline HCl in one ounce of oral pediatric suspension--about \$4.50.)

Summary of drug costs for treatment of streptococcus infections

<u>Medication</u>	<u>Quantity for 10 Days</u>	<u>Approximate Cost</u>
Bicillin Long-Acting	900,000 to 1,200,000 units	\$1.25 to \$2.50 (to doctor)
Procaine plus crystalline penicillin	Ten 400,000-unit ampules	\$2.50 to \$4 (to doctor)
Penicillin G	Forty 200,000-unit tablets	\$2.75 to \$9
Penicillin V	Forty 200,000-unit tablets or pulvules	\$12 to \$18
Erythromycin propionate or tetracycline	Forty 250-mg. tablets or pulvules	\$18 to \$26

TO PREVENT BACTERIAL ENDOCARDITIS in persons with rheumatic or congenital heart disease, the American Heart Association recommends the prophylactic use of antibiotics before and after surgery and dental extractions or other manipulations disturbing the gums, with the following dosages: For the two days prior to surgery, 200,000 units of oral penicillin four times a day. On the day of surgery, the same oral dosage plus injection shortly before the surgery of 600,000 units of crystalline penicillin and 600,000 units of procaine penicillin. For two days after, the same oral dosage. The recommended oral dosage alone should be given if injection is not feasible. For patients sensitive to penicillin, full dosage of erythromycin propionate or a tetracycline should be given over the five-day period. Where surgery involves the urinary or gastrointestinal tract, a tetracycline should in all cases be given for the five days. (In some communities special distribution programs set up in cooperation with chapters of the American Heart Association make the required drugs available at relatively low cost, or free of charge to needy patients.)